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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/483,543 | 01/14/2000 | Tom MUIR | 600-1-259 | 8524 |

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[REDACTED] EXAMINER

WEBER, JON P

[REDACTED] ART UNIT

[REDACTED] PAPER NUMBER

1651

DATE MAILED: 03/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|--------------------|--------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/483,543 | MUIR ET AL. |
| | Examiner | Art Unit |
| | Jon P Weber, Ph.D. | 1651 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 12 December 2002.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 78-95 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) 95 is/are allowed.

6) Claim(s) 78-93 is/are rejected.

7) Claim(s) 94 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

| | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) Paper No(s). <u>24</u> |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of response with amendments filed on 12 December 2002 has been entered. Claims 78-95 have now been presented for examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 89 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 89 recites that the **enzyme** is a recombinant polypeptide. What is disclosed is that the **peptide substrate** is recombinantly produced and then modified by addition of sensors. This is a **new matter** rejection. The claim **must** be canceled or amended as appropriate to overcome

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this rejection. It is suggested that the claim recite, "the peptide substrate is recombinantly produced".

Claims 78-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 78 recites “functional fragments thereof” which is vague and indefinite because the nature and manner that the functional fragments differ from the peptide substrate itself is unclear. If the fragments are functional peptides they must be peptide substrates within the scope of the claim. As much as anything this appears to be redundant. Accordingly, the metes and bounds of functional fragments as they differ from the peptides themselves are unclear.

Claim 78 recites “otherwise intact” which is confusing because “intact” means unchanged, and since the peptide is to be modified it is not clear how it can be intact at the same time. If it is intended that the modifying enzyme does not hydrolyze the peptide, then the claim should say so. It is noted in this regard that all peptide bonds are hydrolysable with the assistance of some protease. Accordingly, all peptides that have a posttranslational modification site also have a protease cleavage site.

Claim 82 recites “post-translational” modification, which is confusing because post-translational modification can only be performed on a peptide that has been translated from mRNA. It is believed that a post-translational type modification is what is intended.

Claim Rejections - 35 USC § 102

Claims 78-80, 82-88, 90 and 93 are rejected under 35 U.S.C. 102(e) as being anticipated by Pollok et al. (US 6,410,255).

Pollok et al. (US 6,410,255) disclose FRET peptides (optical probes) that are used to monitor posttranslational modification type activity especially on tyrosine (abstract). Posttranslational modifications may be phosphorylation, methylation, ADP-ribosylation, glycosylation, prenylation, ubiquitination, sulfation, and proteolysis (column 8, lines 35-42). In

one embodiment of the optical probe, the polypeptide is modified with a first and a second optical probe that interact by energy transfer (column 3, lines 58-67). The peptides contain both the site for posttranslational modification and the protease site (column 9, lines 38-52) between the first and second probes. The posttranslational activity modulates the protease susceptibility of the peptide. For example, at column 41, lines 19-39, the peptide exhibits different susceptibility when phosphorylated. The peptides are made by chemical or recombinant means. Suitable probe fluorophores are disclosed at column 7, lines 2-12 and at column 19, line 47 to column 20, line 11. Additional modulators of the posttranslational modifying enzyme may be added (column 31, line 40 to column 32, line 23). Monitoring the v-Abl kinase with an optical probe by comparison to a radioactive assay is discussed in example 2 (column 43).

Claims 78-79, 82-88, 90, and 93 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee (US 5,795,729).

Lee (US 5,795,729) discloses enzyme substrates containing reporter and quencher fluorescent probe molecules connected by a suitable linker. The enzyme may be a phosphorylase, *inter alia* (column 6, line 65 to column 7, line 8). The enzyme converts the substrate between a first state and a second state resulting in changes in energy transfer between the two probes (see abstract; figures 1-2). Examples of probes are provided at column 3, lines 54-55. Reporter/quencher pairs are discussed at column 7, lines 22-52.

Claim Rejections - 35 USC § 103

Claims 78-88 and 90-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pollok et al. (US 6,410,255) and Lee (US 5,795,729) in view of Haugland (1992).

Haugland (1992) has been discussed in the Office action of 05 October 2001.

The teachings of Pollok et al. (US 6,410,255) and Lee (US 5,795,729) have been discussed above. Pollok et al. (US 6,410,255) and Lee (US 5,795,729) lack the Crk-II peptide and the specific pairs of fluorophores.

A person of ordinary skill in the art at the time the invention was made would have been motivated to apply the teachings of Pollok et al. (US 6,410,255) and Lee (US 5,795,729) to most any posttranslational modifying type enzyme and with any suitable fluorophore pair because Pollok et al. (US 6,410,255) clearly indicate that the selection of any particular enzyme is an arbitrary matter of experimental design choice as evidenced by the discussions at columns 10-22 and fluorophore pairs are well known in the art as indicated by both Lee (US 5,795,729) and Haugland (1992). Pollok et al. (US 6,410,255) goes on to indicate that the means of identifying the recognition site for the posttranslational modifying enzyme are known in the art and that this is used to design the appropriate peptide.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a peptide such as Crk-II and any particular fluorescence pair to produce a suitable FRET peptide for monitoring a posttranslational modifying enzyme activity.

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The reference to Sparks et al. (WO 96/31625) at page 17 of the response is not understood inasmuch as this reference is not of record.

Persechini (US 6,376,257) disclose FRET peptides comprising two GFP molecules fused to opposite ends a linker peptide that is sensitive to ligand binding, such that ligand binding causes a change in FRET between the two GFP moieties (see figures 1 and 12).

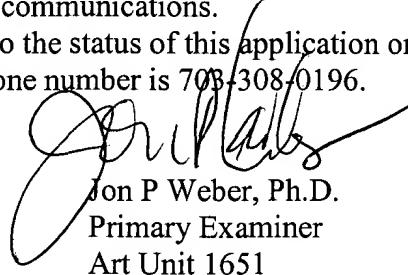
Allowable Subject Matter

Claim 95 is drawn to the same subject matter as canceled claim 50, and is allowable as indicated in the Office action of 03 July 2002.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jon P. Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
March 4, 2003